REMARKS

Claims 1-8 are pending in the above-identified application and stand ready for further action on the merits.

The amendments made herein to the claims do not incorporate new matter into the application as originally filed and entry of the same is thus respectfully requested.

Claim 2 is amended into an independent format by incorporating limitations from claim 1.

Claims 3-4 are amended for purposes of clarify that "each of the outermost layer and the inner layer(s) in which a water-soluble drug is dispersed, contains" a different water-soluble drug (claim 3) or a different concentration of the same water-soluble drug (claim 4).

Claims 5 and 7 are also amended for purposes of clarity only, to recite that "at least one of the outermost layer or inner layer(s) contains two or more water-soluble drugs" based on prior recitations in independent claims 1 and 2.

Claim 6 is amended by inserting a comma "," into the claim so that it's formatting style agrees with the other pending claims.

It is submitted that none of the instant amendments to the claims are narrowing amendments and therefore do not raise issues of prosecution estoppel.

Interview with Examiner

Applicants appreciate the Examiner Neil S. Levy's courtesy in holding a personal interview on December 1, 2005 with Applicants' representative, John W. Bailey. While Examiner Levy is not currently of record in the USPTO as handling the instant case, applicants were able to properly

discuss their concerns as to the outstanding office action and the rejection over Fujioka US '547 set forth therein with the Examiner.

In the Examiner Summary Form, Examiner Levy states as follows:

> *Attorney argues Fujioka requires outer layer, wile Examiner Spear argued obvious to remove, to permit fast release. However, I see the article/device without outer layer as art recognized. Attorney points to pending claims without an outer layer and requiring 2 or more inner layers or multiple concentrations of 1 or more drugs.*

For purposes of clarity, applicants wish to note the present invention as claimed includes the combination of a single outermost layer and a single inner layer (e.g., *see instant claims 1 and 2*), and that such a combination, while not taught or envisioned by Fujioka US '547 can be roughly deemed to correspond to a hypothetical combination of 2 inner layers of the Fujioka US '547 reference, as each of the outermost and inner layer of such a two-layer formulation of the instant invention contains a "carrier comprising a biologically non-degradable hydrophobic polymer material".

Importantly, such a 2-layer hypothetical combination use does *not* include the outer layer of Fujioka US '547, which Fujioka US '547 deems *essential* to achieve its desired object of providing "a drug-delivery formulation which releases a water-soluble drug intracorporeally over prolonged periods of time at a nearly constant rate (zero-order release) with the goal of producing sustained therapeutic efficacy." (*See col. 3, lines 61-65 of Fujioka US '547.*)

More particularly, unlike the present invention, the outer layer of Fujioka US '547 is comprised of a biocompatible material that surrounds the circumference of the said inner layer, is impermeable to water, and is capable of controlling the swelling of the inner layer. As such, even though Examiner Levy may properly recognize that drug formulation (1) of Example 1 of Fujioka

US '547 (*disclosed at column 9, lines 45-56 of Fujioka US '547*) is art recognized, nevertheless the drug formulation (1) of Example 1 of Fujioka US '547 is *not* the present invention, and its disclosure in Fujioka US '547 provides no motivation that would allow one skilled in the art to arrive at the instant invention as claimed, since the drug formulation (1) of Example 1 of Fujioka US '547 is a single layer formulation comprising a biologically non-degradable hydrophobic polymer material as a carrier. The present invention in contrast to Fujioka US '547 contains at least two layers (i.e., an outermost layer and at least one inner layer (*see claims 1 and 2*)), each of which are drug-containing layers and utilize a "carrier comprising a biologically non-degradable hydrophobic polymer material" and wherein the inner layer(s) contains a water-soluble drug, which is different or different in concentration thereof from the drug contained in the outermost layer is contained.

When combined with a full consideration of the above comments, it is submitted the Examiner's comments in the Interview Summary Form resulting from the December 1, 2005 interview correctly state the focus of discussions held between Examiner Levy and the undersigned.

Claim Rejections Under 35 USC § 103

Claims 1-8 have been rejected under 35 USC § 103(a) as being unpatentable over Fujioka et al. US '547 (US 5,851,547) alone. Reconsideration and withdraw of this rejection is respectfully requested based on the following considerations.

Legal Standard for Determining Prima Facie Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge

generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee,* 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The Present Invention and Its Advantages

The present invention provides for controlled release preparations having multi-layer structures. The preparations more particularly relate to controlled drug-release formulations having multi-layer structures, wherein one or more drugs can separately be released with a different behavior *in vivo*, for the purpose of effectively exhibiting the efficacy thereof.

In the present specification, experiments are carried out and reported between preparations of the present invention and comparative preparations. Upon reviewing experiments 1-4 at pages 20-21 of the specification, and Figures 2-5 referred to therein, the Examiner can easily see that the compositions of the present invention possess advantageous properties, and allow one to easily release one or more drugs separately with different behaviors in vivo.

Distinctions over Fujioka et al. US '547

The formulation of Fujioka et al. contains a "water-soluble drug" in an inner layer (claim 1, paragraph (a)). The release mechanism of a water soluble drug dispersed in a hydrophobic polymer is based on "**channeling and cracking phenomenon**" (column 1, lines 47-56, and column 8, lines 61-64). In the Fujioka et al formulation, only an end(s) of the inner layer comes into contact with the external environment, and as a result only a limited region is initially subject to channeling (Column 9, lines 1-6). In addition, the outer layer, due to its characteristic functional design, is able to exercise suitable control of inner layer cracking (column 9, lines 6-8). The outer layer can control water infiltration of inner layer (column 5, lines 10-11) through control swelling thereof (column 5, lines 16-19). Also, the outer layer is ***essential*** to prevent a very rapid initial release of the drug (column 10, lines 9-12). Through these means, the formulation of Fujioka et al. is able to exercise suitable

control of water infiltration into the inner layer and is thereby able to achieve long-term zero-order release (column 9, lines 8-11).

The Examiner's reasoning in setting forth the instant rejection appears to be that it would have been obvious to a person skilled in the art to delete the outer layer (b) of Fujioka formulation (especially that of Fig. 2B) to modify the release of a multilayered rod shaped drug formulation. The Examiner asserts in the Office Action that based on Fig. 3 of Fujioka, which shows the results of the comparison between a matrix formulation (1) and the Fujioka formulation (2) of Fujioka Example 1, it would have been suggested to a person skilled in the art that elimination of the outer layer (b) of Fujioka would provide a more rapid release of the drug (page 3, lines 3-5 and 12-13 of the Office Action).

Applicants believe that the Examiner's assertion contradicts what a person skilled in the art understands, and further, is based on an impermissible level of hindsight reconstruction as explained below.

The Fujioka formulation contains the outer layer (b) as an ***essential*** element, and thereby, water-soluble drug is released at a substantially constant rate (*see abstract and claims of Fujioka*). A person skilled in the art who has read Fujioka should have understood that the outer layer (b) is essential for achieving the constant release desired by Fujioka, and therefore, should *not* eliminate the outer layer (b) of Fujioka, as the entire purpose of using/choosing a Fujioka formulation would be destroyed and/or contradicted by eliminating the outer layer (b) of the Fujioka formulations.

Further, the comparison between the matrix drug formulation (1) and drug formulation (2) in Example 1 of Fujioka (*see column 9, lines 45-63*) and Fig. 3 of Fujioka supports the fact that there exists a contradiction between the Examiner's assertion in the office action and what a person skilled

in the art understands. In the Fujioka Example, the matrix formulation (1) has only one layer that contains a water-soluble drug. Such a matrix formulation was well known to a person skilled in the art (*e.g., see the formulations disclosed in US 4,985,253 and JP 62-174031A that were earlier submitted in an Information Disclosure Statement in the present application*).

Therefore, a person skilled in the art who has seen Fig. 3 of Fujioka should have understood it as indicating that the addition of Fujioka's layer (b) to an otherwise well known matrix formulation enables one to *control release of water-soluble drugs at a substantially constant rate*.

Accordingly, for a person skilled in the art to read "a more rapid release" effect, that person skilled in the art should have to necessarily go back to the well-known matrix formulation (1), by removing the outer layer (b) of the constant release Fujioka formulation (2). This is clearly *not* what Fujioka teaches; instead, it is what Fujioka teaches away from.

As such, Applicants do not find any evidence to support an assertion of any motivation to remove the ***essential*** outer layer (b) of the Fujioka formulations, since removing the outer layer (b) is contrary to all of the teachings of Fujioka and at the same time destroys the intended object of the Fujioka formulations of providing "a drug-delivery formulation which releases a water-soluble drug intracorporeally over prolonged periods of time at a nearly constant rate (zero-order release) with the goal of producing sustained therapeutic efficacy." (*See col. 3, lines 61-65 of Fujioka US '547.*)

The Examiner nonetheless explains in the outstanding Office Action, at page 3, line 19, to page 4, line 3, that it is obvious to delete the outer layer (b) of Fujioka. However, the only citation provided for this contention is Fujioka Column 5, lines 10-15. However, in that part of Fujioka, the only provided disclosure is that the release rate of a water-soluble drug is controlled through control of water infiltration, e.g., by the selection of the outer layer material or the thickness of the outer

layer. Considering the significance of the presence of the ***essential*** outer layer (b) in Fujioka, as explained above, it is submitted that any teaching in Fujioka regarding changing the thickness of the ***essential*** outer layer (b) cannot be said to include an omission of the ***essential*** outer layer (b), and therefore, it is submitted that no disclosure is provided in Fujioka that would motivate one skilled in the art to delete the outer layer (b).

As no evidence to support deleting the outer layer (b) of Fujioka is found in Fujioka US '547 nor any other reference of record, it cannot be said that it would be is obvious for a person skilled in the art to delete the outer layer (b) of Fujioka.

As explained above, when a person skilled in the art reads the Fujioka disclosure, "a more rapid release" effect would not have been picked up upon by a person skilled in the art. It is submitted that only one reason exists for someone to pick up upon the idea of "a more rapid release" effect from the Fujioka disclosure, that reason being the reason of hindsight reconstruction (after reading the present specification). Without the specification of the present application before him, no motivation exists in the teachings and disclosure of Fujioka US '547 that would allow one skilled in the art to arrive at the instantly claimed invention. Thus, it is submitted that the ground of rejection, as stated by the Examiner in the office action, relies on an impermissible level of hindsight reconstruction.

As stated in M.P.E.P. § 2142, "[t]o reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure

must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art."

As also stated in M.P.E.P. § 2141.01 III., "[i]t is difficult but necessary that the decisionmaker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)."

The Examiner asserts, "the omission of an element and its function is obvious if the function of the element is not desired". However, in the instant case, as explained above, the function of the element is only found to be undesirable, after a person skilled in the art has been able to read the present specification. Further, it is submitted that the United States Patent Office Board of Appeal decisions and CCPA decisions cited by the Examiner in the outstanding office action at page 3, lines 15-18 are inapplicable to the fact pattern of the present case. This is because none of the cited decisions say that the "omission of an essential element of the cited art is obvious where removing that essential element destroys the objects and goals of the teachings of the cited art."

As stated in M.P.E.P. § 2143.01 V., "[I]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed.

Cir. 1984) (Claimed device was a blood filter assembly for use during medical procedures wherein both the inlet and outlet for the blood were located at the bottom end of the filter assembly, and wherein a gas vent was present at the top of the filter assembly. The prior art reference taught a liquid strainer for removing dirt and water from gasoline and other light oils wherein the inlet and outlet were at the top of the device, and wherein a pet-cock (stopcock) was located at the bottom of the device for periodically removing the collected dirt and water. The reference further taught that the separation is assisted by gravity. The Board concluded the claims were *prima facie* obvious, reasoning that it would have been obvious to turn the reference device upside down. The court reversed, finding that if the prior art device was turned upside down it would be inoperable for its intended purpose because the gasoline to be filtered would be trapped at the top, the water and heavier oils sought to be separated would flow out of the outlet instead of the purified gasoline, and the screen would become clogged.)."

Further, as stated in M.P.E.P. § 2143.01 VI., "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the

primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.)."

In opposition to the above patent examining guidelines set forth in M.P.E.P. § 2143.01, the Examiner instead relies upon guidelines set forth in M.P.E.P. § 2144.04 II., for the assertion that "omission of an element and its function is obvious if the function of the element is not desired" and additional cites decisions from this portion of the M.P.E.P. to support that position. However, it is submitted that the decisions relied upon by the Examiner, relate to obviousness situations where there is a similarity in purpose/effect between the prior art and invention sought to be patented, without any weighing of the significance of the element to be deleted from the prior art for the purpose/effect of the cited art. Thus, it is submitted that such decisions are not applicable to the fact situation of the present case.

More particularly, Applicant's comments on the inapplicability of the cases cited by the Examiner to the present fact situation are set forth below.

***Ex Parte Wu**, 10 USPQ2d 2031 (Bd. Pat & Inter. 1989)*

Ex Parte Wu says "it would have been obvious to omit Murdock's polybasic acid salts when the function attributed to these salts is not desired or required". However, the prior art Murdock discloses is an "anti-corrosion" composition and the purpose/effect of the inventive composition of Wu relates to "decreasing corrosion", which is in common with the purpose/effect of the Murdock composition. As the decision points out that "Murdock teaches that these salts are beneficial when the composition is employed in contact with fresh water", it is clear that the decision was made based on the recognition that the polybasic acid salts are an optional element for an additional

benefit. Thus, the omission of the salts does not contradict with the purpose/effect of the prior art composition, i.e., "decreasing corrosion". On the other hand, in the present case, the Fujioka formulation is designed for the release of a water-soluble drug at substantially constant rate and layer (b) of Fujioka is an essential element in the provided formulations for achieving this goal or purpose. Therefore, it is submitted that the omission of such an essential element from the prior art, in order to assert a prima facie case of obviousness is not justified by the decision of *Ex Parte Wu.*

***In re Larson**, 340 F.2d 965, 144 USPQ 347 (CCPA 1965)*

As for *In re Larson*, both the prior art of Le Clair and the invention sought to be patented are concerned with a fluid carrier. The difference between them is that the Le Clair carrier additionally has two solid axels. However, from the function of such additional axels, i.e., "increases the cargo carrying capacity", it is clear that the omission of the axels does not contradict with the common purpose/effect to be a fluid carrier. Therefore, it is submitted that the decision in *In re Larson* cannot be relied upon to justify omission of an element from Fujioka that that is essential to the purpose of the provided Fujioka formulations. The decision in *In re Larson* also indicates that there is other evidence to support a finding of obviousness, i.e., other description occurring in La Clair and another piece of prior art (Arpin).

***In re Kuhle**, 526 F.2d 553, 188 USPQ 7 (CCPA 1975)*

As for *In re Kuhle*, prior art references Smith and Sherrard disclose a conductivity meter, which operates on basically the same principle and in the same manner as the invention of Kuhle. The difference between them is that Smith and Sherrard have a switch member, while the Kuhle

device does not have it. However, considering the function of the switch member in a conductivity meter, it is clear that the omission of the member does not contradict with the common purpose/effect to be a conductivity meter, so that it also follows that the decision of In re Kuhle is not applicable to the present situation, where motivation is asserted to exist in the cited art, to delete an essential outer layer (b) of Fujioka, which would if deleted turn destroy the intended function of Fujioka's formulations.

Additional Considerations

No where in the outstanding office action has the Examiner cited any disclosure from the cited Fujioka US '547 reference (or any other reference) that teaches, provides for, or would otherwise lead one of ordinary skill in the art to arrive at the invention recited in pending independent claim 2, which recites the invention of claim 1 and additionally "wherein, a layer consisting of only biologically non-degradable hydrophobic polymer material exists between the one or more inner layer(s) in which a water-soluble drug is dispersed and the outermost layer, or between two inner layers in which a water-soluble drug is dispersed."

Additional Comments

In the interview held with Examiner Levi on December 1, 2005 at the USPTO, Examiner Levi verbally queried the undersigned as to whether English translations of two references listed in the International Preliminary Examination Report for PCT/JP99/02594 could be submitted by the Applicants. Particularly, Examiner Levi wanted to know if English language translations of Document 1 (JP 8-331996) and Document 2 (JP 7-187994) listed in the International Preliminary

Examination Report for PCT/JP99/02594 could be submitted to the USPTO. {The current application is the National Phase Application of PCT/JP99/02594.}

It is the understanding of the undersigned that English translations of JP 8-331996 (Document 1) and JP 7-187994 (Document 2) are not currently available, but that at least two United States Patents have already been considered by the USPTO in the matter of the instant application, which correspond to the two noted Japanese references. Specifically, JP 8-331996 (Document 1) is submitted or believed to correspond to US 5,776,481 (which has already been considered by USPTO) and JP 7-187994 (Document 2) is submitted or believed to correspond to US 5,851,547 (which has already been considered by the USPTO).

CONCLUSION

Accordingly, based upon the above considerations, the Examiner is respectfully requested to reconsider the outstanding rejection under 35 USC § 103 and to issue a Notice of Allowance clearly indicating the patentability of each of pending claims 1-8.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Dated: December 22, 2005

Respectfully submitted,

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